

## CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS

*Transcription of a Panel Meeting on Therapeutics\**

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MODERATOR KNEELAND: It is a pleasure to welcome you here to the Monthly Panel Meeting on Therapeutics for the General Practitioner. The brochure which you all have in hand gives the panel members; however, I shall briefly introduce us. I am the Moderator, and I am in that happy position of having a panel of such bona fide experts that I shall not be required to say anything myself. At the extreme left is Dr. Alban L. Barach, of Columbia University, the College of Physicians and Surgeons, whose work, I am sure, is familiar to all; Dr. David Habif is sitting second from the right; Dr. Habif, oddly enough, is a surgeon, and for several years now has been in charge of many of the antibiotic studies in surgical infections at the Presbyterian Hospital; Dr. Walsh McDermott is seated between Dr. Habif and Dr. Barach; it may surprise you as you look over this program to realize that a relative outsider is on the platform, but Dr. McDermott is not really an outsider, because he is a graduate of the College of Physicians and Surgeons, now temporarily residing at our sister institution on the East River; and Dr. Harry M. Rose, next to me, is Professor of Microbiology at the College of Physicians and Surgeons.

I am sure many questions will occur to you, and we shall be delighted if you would jot those down and give them to the usher. Meanwhile I should like each of these gentlemen to say a few well chosen words, and I shall start with Dr. Harry Rose, who is going to give us some of his mature reflections on antibiotics as they appeal to the microbiologist.

DR. HARRY M. ROSE: Although there have been remarkable advances in all branches of medical science during the past two decades there is probably no area in which progress has been so rapid or far-reaching as in the field of infectious diseases. The introduction of many effective chemotherapeutic agents or antibiotics and the general improvement of diagnostic laboratory procedures have provided means whereby the majority of the common bacterial infections may be cured or controlled. This is indeed so true today that the feeling unfortunately has become rather widespread in certain quarters that infectious diseases actually no longer present a significant problem. In consequence there is a certain lack of interest among practitioners, and this has bred, to some degree at least, an ignorance of the proper use of antibiotic drugs and of diagnostic procedures. As one example, I think we can cite the indiscriminate use of antibiotics, which unfortunately is rather widely

practiced at the present time. Actually, in spite of all the great advances which have been made it is of the utmost importance to the practicing physician that he know a good deal about the nature and the range of action of the different antibiotics which are commonly employed in clinical practice. He must know something about the characteristics of their effects on bacterial agents. He must be familiar with their toxic potentialities. He must understand the most effective ways of using them either singly or in combination. Last, but not least, he must know when not to use antibiotics as well as when to use them.

Before we get on farther into the more clinical part of this discussion by the other members of the panel, I would like to enter a plea for more adequate bacteriologic diagnosis in cases of apparent infectious disease. All too frequently the physician fails to obtain adequate or proper specimens before he initiates therapy with one or more antibiotic drugs. This, in my opinion, is most unwise and most unfortunate. If he does not have an adequate bacteriologic diagnosis he is hard put in many instances to select the best drugs which are to be used in the management of the individual patient. In addition, in certain instances he may find that sensitivity tests are subsequently required, and if the etiologic agent or agents have not been isolated beforehand such tests can not be carried out.

Going back to the list of items I referred to a moment ago, I might say from personal experience that it is astonishing how little physicians know in general about the spectrum of activity of the commonly used antibacterial agents. Some think, for example, that penicillin has a wide range of effect, whereas its clinical activity is entirely confined to the infections caused by gram-positive microorganisms. Some are totally unfamiliar with the range of activity of the less commonly used antibacterial agents such as neomycin or polymixin-B. Many are unfamiliar with cross-resistance to antibiotics, and in ignorance, they pursue therapy with an agent which is valueless because cross-resistance to it has developed through the prior administration of another drug. An example of this would be the administration of Terramycin to an individual whose microorganism had become resistant to Aureomycin.

The physician should understand the difference between a bacteriostatic and a bactericidal agent. Some of the commonly used antibiotics are solely bacteriostatic as used clinically whereas others are bactericidal. These effects are usually demonstrated by sensitivity tests,

as illustrated in the first slide.

(Slide) Here you will observe a plate on which a bacterium has been cultured and two discs containing antibiotics have been placed. There is a wide zone of inhibition of bacterial growth surrounding each disc. This is the so-called disc plate method of testing bacterial sensitivity to antibiotics and is the most widely used test in diagnostic laboratories. Tests of this sort give us some idea what the sensitivity of any given bacterium may be to the effect of any given antibiotic, but I should like to emphasize that the results are crude at best and frequently are unreliable. Many factors enter into this. We don't have time to go into them this afternoon, but among them I can mention the type of media which is employed and the size of the inoculum.

In many cases the disc plate sensitivity test is supplemented by the so-called tube dilution test, as shown in the next slide. (Slide) Here is a series of tubes containing different amounts of antibiotic ranging in concentration from 0.5 to 5 micrograms per milliliter, and you will observe that there is a cutoff point with respect to turbidity in the tubes. The end point dilution is taken as that which contains the smallest amount of antibiotic which prevents the appearance of visible turbidity, and this is usually read as the sensitivity level. In this particular instance it is 2.5 micrograms per milliliter. This, however, merely indicates how much of an antibiotic in a given medium under given conditions over a given period of time will prevent the multiplication of the bacteria to the point of visible turbidity. It is, in other words, a bacteriostatic test. It does not indicate whether the organism actually has been killed at this particular concentration or not.

A further test may be done as shown in the next slide where we see a comparison between the bacteriostatic and bactericidal end points. The sensitivity of a strain of *Streptococcus fecalis* is being examined. In the top row of tubes there is a series of dilutions of penicillin ranging from .02 to 30 units per milliliter. Visible growth is observed in the tubes up to and including 0.1 unit of penicillin per milliliter, but no visible growth is seen thereafter. The sensitivity level would therefore be reported as 0.2 units penicillin per milliliter. However, when subcultures were made from all these tubes into fresh media, it was found organisms were present in all the original tubes up to and including 10 units of penicillin per milliliter, and the first tube in which there was a bactericidal effect was that which contained 15 units of penicillin per

milliliter. There is, obviously, a wide difference between the bacteriostatic and the bactericidal end points. If the bacteriostatic end point were taken as the level at which the organism might be inhibited when treating the patient, one might conclude that relatively small doses of penicillin would be sufficient for therapy. In actual point of fact much more penicillin probably would be required. There are several types of infection in which it is important for us to know bactericidal end points in order to calculate therapy. The outstanding one, of course, is subacute bacterial endocarditis. Another example is certain infections of the urinary tract. In both bacterial endocarditis and infections of the urinary tract the defensive mechanisms of the host are not being brought to bear properly upon the infection. Bacteriostasis is not sufficient for cure. One must choose an antibacterial agent or combination of agents which will kill the organism rather than merely suppress its multiplication.

It goes without saying, of course, that physicians must be fully aware of the toxic potentialities of the various chemotherapeutic agents, and it is not my place to comment further on this point.

The physician should also know when it is appropriate to use antibiotics singly or in combination. In connection with the combined use of antibiotics there has been a good deal of comment concerning the synergistic action of antibiotics on the one hand and their antagonistic action on the other. That synergism may occur and be made use of clinically, there is no question. Antagonism, in my opinion at least, is another matter. It is true that antagonistic effects of antibiotics can be shown experimentally under carefully defined conditions, but it is doubtful whether antibiotic antagonism occurs very often at the clinical level.

Lastly, I should like to mention the fact that it is just as important for the clinician to know when not to use antibiotics as when to use them.

MODERATOR KNEELAND: I am a fully licensed physician, and occasionally I practice a little medicine. Dr. Rose has suggested that I don't use these agents very well. For that reason we have imported Dr. Walsh McDermott, who is one of the foremost students in the field of infectious diseases in this country, and I should like to have him illustrate what some of his views are in regard to antibiotics in internal medical diseases.

DR. WALSH McDERMOTT: Dr. Kneeland, from my long acquaintance-ship and friendship with Dr. Rose, it is only natural that I would know that I would be in no serious disagreement with him; nevertheless I do take issue with him on one point, and have a slight difference in emphasis perhaps on another point. The point on which I take issue is his statement about the improvements in diagnostic methods which we have seen in recent years. I quite agree with him that there have been very many improvements, but I would like to point out that almost without exception these improvements have to do with retrospective bacteriologic diagnosis, and we have seen no improvements in what we most desire, namely, diagnostic methods which are available to the clinician in proper time to be of real value.

Let me particularize on this. We are in a situation which occurs not infrequently in technologic development, where our power far outstrips our knowledge as to how to apply that power. We have the power in the form of these drugs, and we know that if the drugs are to be of maximum benefit they should be used when the patient is sick and not five or six days later. We also know that there are so many drugs that unless we know the identity of the infection in question we cannot make an intelligent choice of drug, yet we have no way of establishing that identity of infection for perhaps twenty-four hours or forty-eight hours, and in some instances four, five or six days thereafter. What are we going to do in such a situation? It seems to me that the only thing we, as physicians, can do is to become more perceptive clinicians and to learn how to draw shrewd microbiologic inferences from clinical phenomena, and use those inferences (at the same time taking the specimens for tests, as Dr. Rose pointed out) at the clinical level to give us help in that most important of all choices, namely, what drug or drugs shall be used in the treatment of that patient now, and not four or five days later when one has the culture.

The other point on which I take some issue with Dr. Rose has only to do with the question of emphasis, and I am pretty sure we have no fundamental disagreement here. We were discussing this matter before the panel meeting started. I realize that I may be guilty of making outrageous statements, but I told him only semi-facetiously that I thought if the doctors of America would stop being drug-sensitivity-test-happy, and pay very little attention to such things, that we would all be better off. I am particularly glad that he has taken so much trouble

to point out how one can become confused by these sensitivity tests, indeed to the point where there are really very few situations in which it makes sense to use them. The difference in emphasis has to do with the terms "bactericidal" and "bacteriostatic." As Dr. Rose pointed out, these are phenomena which apply to certain carefully specified in vitro conditions. They do not necessarily apply to situations which obtain in the body, and I think great harm has been done in all our thinking by too much preoccupation with the notion of whether a particular drug eradicates infection or merely suppresses it. In actual fact, with relatively few exceptions, as all of us know, it is a very difficult thing to drive an infection out of the body.

I think I can sum up, Mr. Chairman, by saying that I believe we should face up to the fact that we don't have proper diagnostic methods to be used in proper time, and that our only recourse until such methods are available is to become better clinicians, and choose wisely and shrewdly on the basis of clinical phenomena.

**MODERATOR KNEELAND:** The internist approaches the problem of antibiotic therapy thinking mainly in terms of therapeusis either in acute overpowering or chronic disorders. Our surgical confreres have a different point of view in certain respects, and they are concerned to a much greater degree, I think, than we in medicine with the preventive or prophylactic use of antibiotics. In consequence, I have found that there is a slight divergence of view, say, between the eighth floor of Presbyterian Hospital and the twelfth floor, which cannot be accounted for on the basis of mountain sickness on the part of the surgeon. I would like Dr. Habib to comment on the use of antibiotics in surgery.

**DR. DAVID HABIF:** There is no question about the fact that antibiotics have changed the field of surgery considerably in that they made major surgery safer with a minimum of complications of infection. It is also clear that antibiotics are adjuvants of good surgery. They have prevented the formation of pus in many cases of cellulitis.

Antibiotics are primarily for the treatment of cellulitis whether the cellulitis is in the form of lymphangitis, pneumonitis, or osteomyelitis. On the other hand, the proper treatment for a collection of pus of moderate or large size is surgical drainage—with few exceptions, such as joint fluid collections and empyemas. These may be treated by repeated aspiration and instillation of antibiotics as well as giving systemic antibiotics. At times, surgical drainage may be indicated for these as

well. Reports in the literature concerning the successful treatment of large collections of purulent material with systemic antibiotics alone are exceptions. The treatment of established infection with a localized collection of pus is drainage.

As a corollary to this, surgeons appreciate a point which some practitioners are apt to forget. Pus tends to form within a period of three to five days. We have all observed the fact that antibiotics will control or remove cellulitis in the presence of pus so that the collection of pus is masked. The otolaryngologist encountered this with the mastoid problem. Beware of deep seated infections, as for example in the breast, which do not respond promptly within five days to antibiotic therapy. There may well be a collection of pus requiring surgical drainage.

Antibiotics are often employed to prevent infection following surgery particularly where mucous membrane-lined organs are cut across as in the lung, esophagus and remainder of the gastrointestinal tract. Here there is endogenous contamination as well as exogenous from the skin, air and possibly, upper respiratory tract of personnel in the operating room. Bones and joints do not have much power to prevent infection developing where there has been heavy contamination. Antibiotics used prophylactically as adjuvants of good surgery aid in a successful outcome without infection. The period of use prophylactically should be three to five days. The appearance of fever or its persistence where no other cause is apparent usually implies a collection of pus which is often masked because cellulitis has been abolished by antibiotics. Cancelling the antibiotic and allowing the cellulitis to return so that the collection of pus becomes clinically apparent is often more rewarding than increasing the dose, adding another, or replacing the drug. Most collections of pus are on top of the deep fascia and surgical drainage leads to a prompt recovery.

Let us consider the choice of antibiotics in surgery. Most surgical infections are due to gram-positive organisms,—predominantly, hemolytic *Staphylococcus aureus* and the streptococci. There is a growing number of infections due to the gram-negative organisms of the coli-aerogenes group. Penicillin is the best agent for hemolytic streptococcus, since one does not encounter resistance. The solution of the problem is not so easy with staphylococcus. Balbina Johnson found that 20 per cent of the staphylococci recovered from infections seen in the minor surgery clinic at the Presbyterian Hospital are resistant to the average

dose of penicillin, whereas 40 per cent of those recovered from in-hospital infections are resistant. This is most probably due to removal of the sensitive strains of these bacteria so that many of those remaining in the air and in the upper respiratory tract are of a resistant type. Exposure of a bacteriological plate for two hours in a surgical ward followed by incubation and sensitivity testing of the staphylococci reveals that better than 90 per cent are resistant.

Because of the finding of gram-negative organisms in many surgical infections, the combination of procaine penicillin and streptomycin is used. Streptomycin is a good drug and has a synergistic effect with penicillin. Unhappily, approximately 25 per cent of both gram-positive and gram-negative organisms develop some resistance to streptomycin within a period of five to seven days. We have given 300,000 units of procaine penicillin and 0.5 gm. of streptomycin every twelve hours.

As an alternative, or as a primary choice, the so-called broad-spectrum antibiotics namely, oxytetracycline (Terramycin), chlortetracycline (Aureomycin) and chloramphenicol (Chloromycetin) may be used. More recently, tetracycline has been made available and sold under the trade names of Achromycin and Tetracyn. The point has often been belabored that these agents are bacteriostatic and while this is true, they are nevertheless highly effective. Both bacteriocidal and bacteriostatic antibiotics are dependent upon host resistance, antibody reaction and the white blood corpuscles. It is interesting that the dose of broad-spectrum antibiotics employed today is defined more by that amount tolerated by patients in general without undue toxicity rather than correlation with sensitivity testing and blood levels obtained. Indeed, this correlation is often poor and one finds that a lower blood level in the serum than needed in the test tube to inhibit bacterial growth will often result in cure. As an example, a patient at Presbyterian Hospital with an *E. coli* septicemia secondary to a kidney infection was cured with Terramycin when the serum level achieved was 1 microgram per milliliter while 4 micrograms per milliliter were needed in vitro.

In 1952, we began using small doses of Terramycin both for prophylactic and therapeutic use. At that time the average dose in general use was 2 grams per 24 hours. We arrived at a dose of 250 milligrams every 12 hours and have continued with this schedule since then. The toxicity with this dosage has been 7 per cent. The serum levels vary between 0.6 and 1.2 micrograms per milliliter. We have had considerable experi-

ence as well with the intramuscular preparation of Terramycin using 100 gm. every 12 hours. The toxicity has been 3 per cent. A similar dosage schedule was followed with Aureomycin, but 1 gram per 24 hours was used for Chloromycetin because of its slightly more rapid excretion. We have used tetracycline in a dose of 250 milligrams every 12 hours by mouth with gratifying results. An intramuscular preparation of tetracycline has not been made available as yet.

In the treatment of cellulitis antibiotics may be selected for convenience by the physician engaged in outpatient practice. The importance of identification of the organism and its sensitivity has been emphasized and should be stressed. However, where culture may not be obtained and therapy is empirical and where pus has not formed as yet, a clinical response may be expected in 24 to 72 hours. This implies that the organism is sensitive to the antibiotic which is making contact. If this favorable response is not forthcoming, it is wiser to change to another agent rather than increase the dose. The possibility of a purulent collection should always be kept in mind and looked for. I must take some issue with Dr. Rose as regards the disc method of testing sensitivity. We believe this gives us a reasonably reliable guide as the expected response to an average dose of the antibiotic employed.

As to the other antibiotics, we have used neomycin orally for sterilizing the gastrointestinal tract, in some instances with bacitracin. It is an excellent drug for use locally in a 1 per cent concentration, but its toxicity prevents its parenteral administration. We have used polymyxin-B sulfate, both parenterally and locally for infections caused by gram-negative organisms; most notably *Bacillus pyocyaneus*. Its neuro- and nephro-toxicity resulting from parenteral use is tolerable and readily controllable. Erythromycin has also been used considerably for infections caused by hemolytic *Staphylococcus aureus* particularly where resistance to penicillin is demonstrated. Bacitracin is an excellent drug for both systemic and local use. Nephro-toxicity resulting from parenteral use is readily managed as indicated in many of the writings of Dr. Frank L. Meleney. It is the agent most frequently used at our hospital for local infections, often in combination with neomycin.

In closing may I say there is no antibiotic which does not have some toxicity. Further, there is no antibiotic to which some bacterial organisms are not resistant within a group which is known to be sensitive. In those instances where cultures are not obtainable, good clinical judg-

ment in observing the response of infection to an antibiotic is mandatory.

MODERATOR KNEELAND: Thank you, Dr. Habif.

Dr. Barach is, as you all know, a man of unlimited energy and ingenuity, having devised machinery which permits people to breathe or to stop breathing, if they prefer to stop breathing. He was one of the great pioneers of oxygen therapy and the absolute inventor of helium for uses other than levitation. His latest contribution is a machine which makes you cough,—the exsufflator which empties your entire bronchial tree. As the result of these interests he has found hanging around his neck a special clinic for patients with chronic intractable pulmonary conditions with which he endeavors to cope. For a number of years, since the introduction of antibiotics, he has accumulated a large experience in the management of chronic pulmonary disease, and has had a really enviable opportunity to observe some of the unfortunate side effects of these agents. I think, perhaps, he might have a few words to say on this subject.

DR. BARACH: Dr. Kneeland, I have been pushed into the field of antibiotic therapy, as you indicated, because many patients with bronchial asthma, emphysema, bronchiectasis and the more chronic infections of the bronchi known as chronic bronchitis without bronchiectatic change, have had pus in their sputum and since I have, reluctantly perhaps, come to some conclusions that don't entirely agree with those of the three speakers who have already presented their wisdom in this field, I feel somewhat out on a limb. Perhaps I might take a minute to remind you of the story of the inebriated gentleman who was walking with a friend and stepped accidentally into an elevator shaft; on his way down he called up and said, "Watch that first step, It's a lulu!" I feel I might be taking a similar step in the presence of these expert bacteriologists. Nevertheless, Dr. Kneeland has given me the opportunity to present our experiences in the treatment of chronic bronchopulmonary disease.

In those cases in which an acute respiratory infection takes place, in an individual not formerly ridden with a suppurative bronchitis, the treatment is generally not too difficult. Dr. McDermott said clinical judgment perhaps might reveal that a broad-spectrum antibiotic like tetracycline administered in a dosage of one gram or more a day for four or five days may result in the clearing of the infection. In order to avoid penicillin allergy, that would appear to be a good way to start.

Our main problems arise in attempts to arrest suppurative bronchial disease in patients with *chronic* pulmonary illness. The problem is especially complicated because almost all of them have an impairment of drainage. An individual may cough up a certain amount of mucopurulent sputum but the secretions retained within the respiratory bronchioles and smaller bronchi maintain the chronic suppurative disease, swelling of the mucous membrane and dyspnea. Although I suppose some of the most dramatic examples of improvement in shortness of breath have taken place after the use of antibiotics, with the increase in the power of these drugs has come increased hazards in their employment.

In a study begun in 1941 on the inhalation of penicillin, we observed a good many individuals who had had chronic bronchitis, bronchiectasis, pulmonary emphysema or pulmonary fibrosis in whom penicillin aerosol resulted in an improvement of dyspnea and decrease in the purulent quality of the sputum. We had no deaths as the result of penicillin administration. In a certain number of cases we observed a Friedländer bacillus infection as revealed not simply by sputum culture but by the sudden appearance of increased quantities of yellow pus in the sputum, an occurrence described also by Weinstein. In these individuals the use of broad-spectrum antibiotics, preferably combined with streptomycin for six days, resulted in all of our cases in the elimination of that particular organism.

Some of our patients in whom penicillin, either by mouth or by aerosol, had been used for four to seven years were brought into the hospital in an attempt to rid them entirely of all suppuration. Broad-spectrum antibiotics like Terramycin were employed intravenously and by mouth in large doses. After temporary, dramatic improvement, some of those patients were readmitted to the hospital two weeks afterwards with extreme dyspnea and died, within a period of two weeks, of a *Proteus* pneumonia or a *Pseudomonas* infection. These were all cases in which bronchial drainage was severely impaired.

We have been very much interested in Dr. Habib's notion that the pharmacology of Terramycin was not worked out carefully enough. Although we have not found that 250 mg. of Terramycin twice a day was adequate, we have found one gram in four divided doses was effective in most cases. Since using that dosage and with attention paid to the attempt to improve bronchial drainage, we have not had a death

from contaminating organisms. Last week we did observe a death in a patient with lung cancer, and a *Pseudomonas* pulmonary infection developed during broad-spectrum antibiotic therapy.

When our clinical judgment indicates that relief of dyspnea may be the result of decreasing the obstructive element—dyspnea, i.e. by getting rid of infection in the bronchial wall, we are confronted with the problem of how to accomplish this in the patient with chronic suppurative pulmonary disease. In our clinic we have abandoned the use of intramuscular penicillin because of the steadily increasing number of allergic deaths and because, for the treatment of penicillin sensitive organisms in the respiratory tract, a million units orally twice a day gives an adequate blood level, according to the studies of Bunn, Pulaski and ourselves,—provided the organism is penicillin sensitive. Since practically all gram-positive organisms except a resistant *Staphylococcus aureus* are penicillin sensitive, that program of oral administration of larger doses of penicillin would appear to be the best because it can be used over a long period of time with very few side effects.

When we see a case in which the sputum, originally pus-containing, has become mucoid and then later suddenly again becomes pus ridden, we are likely to find one of the gram-negative organisms. Under these circumstances a week of broad-spectrum antibiotic therapy may be useful in clearing this invasion. Following this, a return to penicillin treatment is generally indicated. We use the following method of testing organism sensitivity,—Dr. Rose has agreed to do this at the hospital and we use it in the office. We put a swab into a sample of sputum and smear a blood plate with it and then place the sensitivity discs on that sputum smear. The next day, if we find a large area of inhibition around a disc, we can say that the drug that was used, or that the various drugs that showed this inhibiting effect, may be clinically useful. It is certainly important to do that on the *first* sputum sample. If we find, for example, a staphylococcus has been suppressed but *Klebsiella* is growing lightly around the disc that has Aureomycin, we would probably conclude that the staphylococcus was the invading organism. That first sensitivity test is the most important test that one can do. After the patient has had antibiotic therapy, the subsequent sensitivity tests may be very misleading for the reason that one generally finds that effective treatment against gram-positive organisms results in growth of gram-negative flora. We have had a man on penicillin aerosol for ten years whose sputum

regularly reveals colon bacilli on cultures and smears. He has not had a demonstrable infection with colon bacilli. If we then should have been guided by a sensitivity test which showed that this colon bacillus was sensitive to Terramycin, Aureomycin and Chloromycetin, we might have stopped treatment with a relatively innocent drug and used one of the broad-spectrum antibiotics, which are especially useful for actual infection with gram-negative organisms, when the sputum suddenly becomes purulent. However, these more powerful agents should never be used when the sputum is mucoid just because the sensitivity test indicates that the colon bacillus isolated is not sensitive to penicillin.

Let us assume the indication for using a broad-spectrum antibiotic is present. I think the situation has been significantly changed by two developments. The first is that modest advance has been made by the introduction of tetracycline, introduced by Lederle under the name of Achromycin. The studies of a number of people, including Finland, indicate that patients are much less apt to have nausea or diarrhea from this drug, and that cross-resistance and cross-sensitivity are very similar to that of Aureomycin and Terramycin. It may well be that in the great majority of cases tetracycline, in adequate daily dosage of at least 1.5 gm., will be preferred to Terramycin, Aureomycin or Chloromycetin. The second development is an observation that Dr. Hardy of the Lederle Laboratories has brought to my attention. He has noted that diarrhea is not due to monilia but is caused by the irritant effect of the drug on the mucous membrane of the gastrointestinal tract. If the intestinal content of Aureomycin is above 1 mg. per cc. of fluid, it will irritate the gut and cause irritant diarrhea. Later, as ulcerations appear, monilia infections and proctitis in males may occur. Our experience indicates that if a patient takes a full glass of milk,—and there is reason to believe that acidophilus milk containing lactobacilli is preferable,—with each 250 mg. or 500 mg. of drug, diarrhea is much less likely to occur. One would then have the opportunity of giving a drug like tetracycline for a four week period, first 250 mg. six times a day and then after the purulent quality of the sputum became less, three times a day.\* Even with this modest yet definite improvement in the use of broad-spectrum antibiotics, our problems are not solved. We have had

\* With regard to nausea effects, it is useless to compare tetracycline with Terramycin or Aureomycin unless adequate fluids, especially milk, are ingested at the same time.

pseudomonas infections, some of which could not be adequately controlled with polymyxin-B. In some of the patients in whom we have used the exsufflator that Dr. Kneeland was kind enough to mention, a half pint of mucopurulent secretion has been mechanically removed *after* the patient had eliminated as much as he could by his own voluntary cough. It is a very difficult problem to sterilize that amount of infected secretion, the secretion being moved back and forth along the bronchial tree. As many of you know, in cases with impaired pulmonary elasticity and retarded air flow, as in pulmonary emphysema, a vigorous cough will collapse the bronchi and prevent the mucus from coming out. In these cases an effective cough would be characterized by a deep inspiration and *moderately* vigorous cough but not a forceful cough. That type of cough will only deliver mucus from the tracheo-bronchial tree or bifurcation of the trachea upward into the mouth. The mucus in the smaller bronchi is apt to stay there for long periods, as shown by the character of the plugs, unless one uses some other method.

Many have had the experience of having patients die as the result of attempting to sterilize the bronchial tree of known pathogens only to have strains of bacteria, that formerly were rarely or never pathogenic, emerge and become invasive. It emphasizes what Dr. Habif has said about drainage. In the treatment of chronic bronchial infection every effort should be made to increase bronchial drainage; to have the patient, when necessary, sleep with the chest tilted head down at an angle so that gravity will be of help in effecting postural drainage. The lower lobes of the lungs will then be ventilated more effectively by diaphragmatic breathing. Exsufflation with negative pressure consists merely of a full inspiration followed by exposure of the bronchial tree to a negative pressure blower that provides an air wave of high velocity blowing past the mouth or nose, in such a way as to blow the secretions to the upper respiratory tract. You can realize the variety of illnesses in which impaired elimination of bronchial secretion occurs and how difficult is the treatment with antibiotics in chronic illness.

We have stressed the value of diaphragmatic breathing in patients with pulmonary disease. In many of the people in this audience costal breathing may be employed as the result of early training in schools. But the use of the diaphragm is necessary to aerate areas of the lung where bronchial secretions stagnate, namely, the bases of the lungs. An

increased movement of air from the lungs takes place by compressing the lower thorax and upper abdomen in such a way as to increase ventilation of the lungs in patients with pulmonary emphysema and bronchial asthma. Frequently, after inhaling a bronchodilator aerosol, which is one of the methods of opening the bronchi when in spasm, and compressing the chest and lower abdomen ten times during the expiratory cycle, the patient may be able to cough up mucus that was hitherto in the depths of the lungs.

(Slide) This simply is a picture of the result of exsufflation, sudden deflation of the lungs, resulting in air velocities leaving the mouth at two to five times faster rate than patients with chronic pulmonary suppuration can themselves produce.

The G. B. Spencer type of abdominal belt with two springs in it also aids the movement of the lower lobes of the lungs which is the site, in most instances, where suppurative disease is most apt to occur.

In answer to a question which has been submitted regarding the diarrhea which occurs as the result of antibiotic therapy, I would say that when diarrhea does take place as an irritant effect of the broad-spectrum antibiotics on the mucous membrane of the intestine, one should stop the drugs, particularly those that inhibit growth of the colon bacillus, until the diarrhea has been controlled. I think every effort should be made to control it as quickly as possible. I have seen it last as long as five months in people in whom vigorous measures have not been used. It may clear up spontaneously but I think that paregoric, Kaopectate, acidophilus milk and Yogurt might well be used. As to whether or not administration of acidophilus organisms actually has a value, I don't know. I am inclined to believe it does. I think Dr. Habif believes this also, but it is a difficult thing to prove. We did see one man with advanced bronchiectasis die of monilial peritonitis after ten days of vigorous Terramycin therapy,—he had developed ulcers in the large intestine and then monilial peritonitis occurred secondarily as the result of the ousting of the other organisms. They don't cause the diarrhea but they may become invasive on an irritated mucous membrane.

I want to say just two things more. In my opinion penicillin by mouth is the most valuable of the drugs that are the most feasible for long continued therapy. I want to say that in the case of respiratory infection with resistant *Staphylococcus aureus*, which may be resistant to five or ten units of penicillin per cc., and in which resistance to the

broad-spectrum antibiotics like Terramycin and Aureomycin is also present, the most effective way of eliminating the organism is by inhalation of penicillin by aerosol. By this means the concentration of penicillin in the sputum may be raised as high as fifty units or more per cc. of sputum. However, in some instances bronchospasm is provoked. Aerosol penicillin therapy for resistant staphylococcus infections may perhaps best be used in the following way: One million units of crystalline penicillin, dissolved in a mixture of 1 cc. propylene glycol, 0.5 to 1.0 cc. of 2.25 per cent racemic epinephrine and 12 cc. normal saline. Four cc. of this aerosol mixture is administered four times daily. With other non-resistant organisms this dosage, twice daily, is often the most feasible and practical way to control bronchial infection, especially bronchiectasis.

My second thought is that the *Staphylococcus aureus* actually represents the most important problem in chronic pulmonary disease. Chloromycetin is used in our clinic because in many instances sensitivity studies show that staphylococci may be most sensitive to Chloromycetin, and with a week's use the resistant organisms may disappear, and penicillin may again be employed.

We have seen some cases of pneumococcus infection. One case had a *Pneumococcus XIX* with bronchial infection for a period of many years previous. A course of antimicrobial therapy resulted in arrest of what was a chronic long-continued infection, with no recurrence during an observation period of two years. We have also seen patients in whom, with the use of penicillin, the improvement appeared to be linked with the disappearance of the non-hemolytic streptococcus organism.

Erythromycin and Magnamycin in chronic bronchopulmonary infections have been quite disappointing, although at times helpful but in the case of resistant staphylococcus not generally useful for longer than a week. One may then have to turn to a series of antibiotics such as Chloromycetin, or streptomycin with penicillin, or as I said, tetracycline in a dosage of 1.5 to 2.0 gm. if the organism is sensitive. Failing that, if the staphylococcus is still resistant, then at least in bronchopulmonary infections, the patient may need to give a week or ten days of his time and inhale penicillin by aerosol.

**MODERATOR KNEELAND:** A number of questions have come up. Obviously a number of people have been picking on Dr. Rose. Perhaps he would like to do a little rebutting and answer the questions that have

been directed towards the microbiological aspect of the problem.

DR. ROSE: I have four questions, Dr. Kneeland, all of which deal essentially with the same subject, so perhaps I can answer them together. The subject concerns antibiotic synergism and antagonism. As I indicated before, when antibiotics are administered in combination, synergistic effects may be observed with certain combinations and antagonistic effects with others. However, I should like to emphasize that the antagonism between antibiotics which has been demonstrated both in vitro and in vivo, has been so demonstrated under rigidly controlled experimental conditions, under which the levels of the antibiotics varied within fairly narrow limits. When those limits were exceeded the antagonism could no longer be demonstrated. This contrasts with synergism which occurs over a much wider range of antibiotic concentrations. There is reason to believe from experimental evidence, as well as from clinical observation, that antagonism between antibiotics is of little or no consequence in the management of human infections. It is possible, of course, that antagonism may exist occasionally but probably this is a rare phenomenon. On the other hand, synergism can be demonstrated quite regularly and is taken advantage of every day of the week in thousands of instances in the administration of antibiotic combinations. We know very little about the mode of action of these antibacterial agents. We do not understand the mechanisms of antibiotic synergism and antagonism. Perhaps in the future these problems will be elucidated but the answers are by no means apparent at the present time.

I have another question which asks which would be the antibiotic of choice in a urinary tract infection—cystitis—when penicillin, penicillin plus streptomycin and Gantrisin were of no value. It is difficult for me to answer this question because I don't know what caused the infection and I think it exemplifies what I said before about knowing the nature of the causative agent before being able to use antibiotics intelligently. In the case of a urinary tract infection, which apparently is resistant to antibiotic therapy, the best thing is to isolate the organism or organisms from the urine and to run a series of sensitivity tests to discover, if possible, which antibiotic or combination of antibiotics would seem to give the most hope of a cure and then to use that combination. If it does not work, try another. Eventually one may run out of combinations that will influence the infection, but the method that

I have indicated is the only rational one I know.

Dr. McDermott has remonstrated with me in a very mild and gentlemanly manner, as usual, for some remarks concerning sensitivity tests and diagnostic procedures and I must say that to a large extent I concur with his point of view. I still believe, however, that accurate diagnosis is the keystone of therapy and that if the physician does not know what he is dealing with he is like a pilot of a ship who is trying to navigate while blindfolded. There are many instances, to be sure, when the physician will have to rely on his experience and judgment in formulating a program of antibiotic therapy because he can find no way of making a specific bacteriologic or serologic diagnosis. Under those circumstances there is nothing to be done except to employ the antibiotic or combination of antibiotics which seem most logical and to observe whether there is or is not a beneficial response to therapy. Parenthetically, I might say that under such circumstances antibiotic therapy is often continued far too long a time. When antibiotics are administered and the patient does not seem to be responding, when the fever remains elevated and the signs and symptoms continue after a reasonable period of time, it is only logical to discontinue therapy, invoking the second law of therapeutics: If the treatment is not doing the patient any good, stop it.

MODERATOR KNEELAND: Thank you, Dr. Rose.

I cannot resist at this point putting in one little remark myself, which derives from something that Dr. Rose has indicated, and that is the deliberate use of antibiotics as a therapeutic trial in an endeavor to make a diagnosis. It seems to me there is one very important principle here, and that is that one should employ antibiotics in pyrexia of unknown origin in a well thought-out sequence, using the one first with the smallest range of antibacterial action and saving the antituberculosis agents until the last, because if one gets an effect in pyrexia of unknown origin, let us say with streptomycin, there is strong presumption that one may be dealing with tuberculosis, and that being established one is then committed to a long regimen of therapy. *Now Dr. Habib has a question or two, I believe.*

DR. HABIF: I have just one, Dr. Kneeland, and the question reads: What is the status of polymyxin-B? Is it felt that its toxicity should limit its use to severely ill patients? Polymyxin bisulfate is a good agent, which has its greatest usefulness in *Pseudomonas aeruginosa* infections. Its dosage is 2 ½ mg. per kg. of body weight in divided doses given every

eight hours.  $2\frac{1}{2}$  mg. per kilo is the twenty-four hour dosage. When given intramuscularly it is somewhat painful. Its greatest use is in septicemia and in urinary tract infections and also it is of value locally. As to its toxicity, it is neurotoxic and nephrotoxic. It is a long chain polypeptide like bacitracin, and, like bacitracin, if used properly, it may be considered a safe drug and its use need not be restricted only to the very ill patient.

MODERATOR KNEELAND: Dr. McDermott!

DR. MCDERMOTT: I have three questions here, Mr. Chairman. Two of them are on the same point, and one is a separate one. Both have to do with diagnosis, one about bacteriologic diagnosis with particular reference to the expense to the patient, and hence the interference with the clinician's freedom of action, and the other concerns the rationale of doing as so many people do,—i. e., start a patient on a broad-spectrum drug for a few days and switch to erythromycin or Magnamycin with the hope of avoiding the emergence of drug resistance. I think both of those are concerned with the same thing. Insofar as finances go, all diagnostic tests cost money, and we physicians have gradually found that we cannot get them all so we get the particular tests which we believe are worth the money. If they provide information to us of importance to the patient, then they are worth while, and I think in this case, namely, the treatment of a patient with infection, there is no question about the fact that such tests should be obtained. As Dr. Rose pointed out, he and I are in agreement; indeed what we are doing is presenting a three-plank program. He is emphasizing two of the planks and I have been emphasizing the middle plank. Our three-plank program is really, first, that it is of the greatest importance to obtain the specimens for an etiologic diagnosis in every case of an illness which might be an infection, although one must wait for a result until the microorganisms have synthesized enough protoplasm to make themselves seen, which is twenty-four or forty-eight hours, or three or four days. Second, it is likewise of importance to the clinician to start therapy, and start therapy shrewdly. Indeed, we should perhaps be learning more about diseases than we are about drugs at this stage when there are so many drugs. Plank three, which I am particularly glad he emphasized, is stop drug therapy if what you are doing does not make sense. It would be so much better, to draw an extreme case, to give five drugs on day one, if we could only be certain that we would narrow

it down to two, or one on days two or three, on the basis of the information obtained from the laboratory. Instead we make ourselves prisoners of our therapy and proceed to continue therapy with drugs which are no longer of value. Mr. Chairman, I might be accused of speaking in generalities, and if I could particularize I would take one condition.

MODERATOR KNEELAND: Indeed, you may.

DR. MCDERMOTT: Let us assume the physician is called to see a patient with a febrile illness which is in fact pneumonia. What can he do? He certainly can demonstrate that the patient has pneumonia. He does not need a laboratory for that. It is helpful if he can get a total leukocyte count, but we all regard that as one of the essentials in practice these days anyway, and it is not an inordinately expensive procedure. Given those facts he should then obtain material, namely, sputum, blood, and a nasopharyngeal swab for culture, and should proceed to analyze the situation. He has already established the patient has pneumonia; now the next decision he has to make is which drug or drugs is appropriate for this patient's pneumonia and not for all pneumonias. How should he go about that? The first question—and it has to be answered right then and there, not four days later—has to be answered on clinical grounds: Does this patient have a very severe pneumonia, or does this patient have only a moderately severe or mild pneumonia? Certainly that is a decision which all of us are perfectly equipped to make. What difference does it make? A great deal of difference. If the patient has an unusually severe pneumonia, it is our practice to administer streptomycin and penicillin right away for the first night. Why those particular drugs? What could be causing an unusually severe pneumonia? Well, the things which could be causing it are about four or five in number. To the more extremely ill pneumococcal patients, the penicillin would be valuable; in Friedländer's pneumonia, the streptomycin would be of value; in suppurative pneumonia, the condition which gives rise to lung abscess, the two together would be the proper therapy, also in staphylococcal pneumonia. What would be the proper therapy for beta hemolytic streptococci? Penicillin or Terramycin. On the following day, if a diagnosis of Friedländer's pneumonia is made, the culture having grown out (because that is one of the more rapidly growing organisms), one could stop the penicillin and add chloramphenicol, if you will, or one of the tetracyclines. Similarly, if pneumococci were recovered, stop the streptomycin and continue with

the penicillin. This is the manner in which one uses the material gathered before therapy to guide our treatment after the start of the therapy. The important thing is to make one's initial decision on the probabilities as to what this particular clinical syndrome might represent. If the patient has a mild or moderate pneumonia I see no reason then for not giving one of the tetracycline drugs, and no particular reason to choose one over the other. It is established that the tetracycline drugs are as good as penicillin in the treatment of pneumococcal pneumonia insofar as medical recovery is concerned. It has not been established that they are as good as penicillin in preventing pneumococcal meningitis or the other complications, although there is no reason why they are not. So Mr. Chairman, that is the example I would use as to what I mean and what Dr. Rose means by saying that it is important to establish the diagnosis from the laboratory standpoint, but while doing that it is more important to know more about what infections might be present and their clinical manifestations, and to choose drugs accordingly, than it ever was before. The day has long since passed when we can give all the available drugs in the form of one drug, namely, sulfonamide.

The other question was, would the other gentlemen comment on Dr. Barach's statements that tetracycline will replace the other broad-spectrum antibiotics? For myself all I can say is that I have no personal experience. The information which I have heard and read is exactly as outlined by Dr. Barach.

MODERATOR KNEELAND: I think this ends the question period and therefore we can assume this meeting is adjourned.